REMARKS

As a preliminary matter, Applicant's representative, the undersigned, thanks Examiner Haghighatian for courtesies extended during the telelphonic interview of November 1, 2011. During the interview, the rejections of record were discussed, as well as possible amendments to the claims for overcoming same as set forth in the Examiner's interview summary. No agreement was reached.

I. Status of the Claims

By the present communication, claims 1 and 2 are amended to recite "whereby the particle size of the pharmaceutically active agent is reduced by the micronization process." The amendment clarifies that the process brings about a reduction in particle size as a result of the micronization. Claim 7 is amended to correct a grammatical error. New claims 24 and 25 are added. Support for the new and amended claims may be found at paragraphs [0001], [0009], [0025] and [0029] of the (published) specification as filed, and thus no new matter is added. Claims 1-19, and 23-25 remain pending and under examination in this application. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendment and the reasons that follow.

II. Claim Rejections – 35 U.S.C. § 103

(A) Rejection of claims 1-19 and 23 over DeStefano in view of Zhang

Claims 1-19 and 23 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over U.S. Pat. No. 6,135,628, issued to DeStefano *et al* in view of U.S. Pat. No. 6,228,346, issued to Zhang *et al*.. In support of these rejections, the Office argues that

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to have implemented the step of suspending particles in a gaseous propellant or in a compressed gas as taught by Zhang et al with the process of DeStefano et al on micronizing and homogenizing aerosol particulate formulations for

> inhalation with a reasonable expectation of successfully preparing dry powder particles in a suitable particle size with the known process of micronization and high pressure homogenization. Zhang et al teach that the gas system has two functions: to decrease the overall system's vapor pressure and to increase the system's dissolving capacity. In other words, the claims would have been obvious because the technique for improving a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.
>
> From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. (*Office Action dated 8/11/2011, pp. 10-11, citations omitted*)

Applicant respectfully traverses these rejections for the following reasons.

The Office bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). Furthermore, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). This rejection should be withdrawn because the combination of DeStefano and Zhang does not teach or suggest a process for micronization of a pharmaceutically active agent comprising the steps of:(a) suspending the pharmaceutically active agent in a gaseous propellant or in a compressed gas, (b) processing this suspension by high pressure homogenization, and (c) obtaining dry powder upon depressurization; or (c) obtaining a suspension of the micronized pharmaceutically active agent in the gaseous propellant; whereby the particle size of the pharmaceutically active agent is reduced by the micronization process.

In particular, there is no teaching or suggestion in either of the references that the pharmaceutically active agent could be suspended in a gaseous propellant or in a compressed gas,

or that the dry powder is directly obtained upon depressurization, or that the particle size of the pharmaceutically active agent is reduced by the micronization process.

First, as explained in the Amendment and Response dated May 23, 2011, and as acknowledged by the Office on p. 8 of the Office Action, DeStefano lacks teachings on suspending the pharmaceutically active agent in a gaseous propellant or in a compressed gas. Further, contrary to the Office's assertion, this deficiency is NOT cured by Zhang.

Zhang teaches mixing, in a liquid state, gases with low evaporation enthalpy with another gas having high evaporation enthalpy. (Col. 3, lines 5-22.) This propellant mixture may be used "for pharmaceutical aerosols so as to micronize the drugs for pulmonary application." (*Id.*, lines 23-26.) "This propellant mixture is present in the *subcritical state*..." (*Id.*, lines 26-30, emphasis added). The skilled artisan understands that the subcritical state for a gas includes the liquid state. In fact, all of the examples describe that the pharmaceutical compound is dissolved in a liquid mixture by maintaining vapor pressure of 5 to 20 bar. Zhang therefore, fails to remedy the deficiencies of DeStefano and does NOT teach the step of suspending particles in a gaseous propellant or compressed gas, as alleged by the Office. To the extent that the Office relies upon the disclosure of propellant gases in col. 4, lines 5-17 of Zhang, Applicants respectfully submit that the particular recitation relates to the composition of pharmaceutical aerosol in a canister and not to a gaseous propellant or compressed gas used to suspend a pharmaceutically active agent prior to homogenization and micronization to reduce the particle size, as in the presently amended claims.

Further, Zhang lacks specific disclosure on the step of high pressure homogenization. Moreover, contrary to the process of present claims 9-10, Zhang specifically teaches away from the use of halogenated hydrocarbons for the micronization process (Col. 2, lines 40-44).

Furthermore, neither DeStefano nor Zhang teach the that the micronization process enables one to obtain dry micronized powder of the pharmaceutically active agent directly upon depressurization after homogenization, as recited in the present claims. Additionally, both

DeStefano and Zhang fail to teach that the particle size of the pharmaceutically active agent is reduced by the micronization process of the invention, as described in amended independent claims 1, 2 and new claims 24 and 25.

Consequently, even if a skilled artisan were to combine the teachings of DeStefano and Zhang, and use Zhang's propellant gases in subcritical state, into DeStefano's homogenization process, he or she would have failed to arrive at the claimed invention. For at least this reason, a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of this ground of rejection.

(B) Rejection of claims 1-5, 8-12, 15-19 and 23 over Mohsen

Claims 1-5, 8-12, 15-19 and 23 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over U.S. Pat. Pub. No. 20080118442, by Mohsen *et al.* In support of these rejections, the Office argues that

> Mohsen et al do not anticipate the claimed process because the method steps are not disclosed as claimed. However adequate disclosure has been provided to one of ordinary skill in the art to make and use the invention as claimed. Mohsen et al teach inhalation of dry powder formulations comprising suspended active particles in a compressed gas, gaseous propellant or combination thereof in micron size. The suspension is also carried out by homogenization under pressure. ….it would have been obvious to have selected the process steps as claimed from the teachings of the .from within a prior art disclosure, to arrive at a product / process "yielding no more than one would expect from such an arrangement". . (*Office Action dated 8/11/2011, pp. 13-14, citations omitted*)

Applicant respectfully traverses these rejections for the following reasons.

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art teaches or suggests every claim limitation and provide a reason to combine (or modify) the teachings to arrive at the claimed invention with a reasonable expectation of success.

In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. However, Mohsen fails to teach or suggest at least three elements of the claimed process and therefore cannot render the present claims obvious.

First, Mohsen fails to disclose the step of suspending the pharmaceutically active agent in a gaseous propellant or a compressed gas, as in the presently claimed process. Nowhere does Mohsen teach or suggest that the pharmaceutically acceptable propellant used in its formulation is a gaseous propellant or a compressed gas and not a liquid. Indeed the Examples disclosed in ¶¶ [0032]-[0038] of Mohsen disclose filling the reaction kettle by pumping hydrofluoroalkanes (HFA) under pressure and at low temperatures, which indicate that the HFAs are in liquid form. The Office has provided no evidence and articulated no reason as to why one skilled in the art would conclude that the drug particle disclosed in Mohsen would be suspended in a gaseous propellant, as in the presently claimed process.

Second, Mohsen fails to disclose the step of processing a suspension of a pharmaceutically active agent in a gaseous propellant. Mohsen discloses the use of a Silverstone (sonicator) homogenizer for mixing formulations containing hydrofluoroalkane and surfactant. As disclosed in ¶¶ [0033], [0035] and [0037] of Mohsen, "After complete addition of the surfactant, the homogenizer is energized and the mixture is sonicated for approximately 20 minutes.....The sonicator is deenergized and the lighting mixture is energized. The drug powder is added to the vessel and continuously stirred at medium speed." Accordingly, Mohsen only describes the use of a homogenizer to homogenize a mixture of propellant and surfactant before addition of the drug powder.

Third, Mohsen fails to teach a micronization process which enables one to obtain dry micronized powder of the pharmaceutically active agent directly upon depressurization after homogenization, as recited in the present claims 1 and 24. Additionally, Mohsen fails to disclose that the particle size of the pharmaceutically active agent is reduced by the process of the invention, as described in amended independent claims 1, 2 and new claims 24 and 25.

Further, Mohsen's primary focus is on providing pharmaceutical aerosol formulations for a specific pharmaceutically active agent, i.e. dihydroergotamine (Mohsen, abstract and claims). Mohsen neither teaches nor suggests that the process could be used to make aerosol formulations of other pharmaceutically active agents. Moreover, as acknowledged by the Office, Mohsen fails to disclose the method steps as disclosed in the present claims, and the Office has not established a reasonable expectation of success would result from modification of Mohsen's method.

Mohsen thus fails to teach or suggest all the elements of the rejected claims and therefore fails to establish a prima facie case of obviousness. Applicants therefore kindly request the PTO to reconsider and withdraw the rejection.

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Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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